Official Title: Effects of Pain Neuroscience Education and Therapeutic Exercise on Pain, Catastrophizing, Kinesiophobia and Upper Limb Function in Patients With Non-specific Neck Pain.

Brief Title: Effects of Education and Exercise on Pain, Psychosocial Factors, and Upper Limb Function in Non-specific Neck Pain.

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STUDY PROTOCOL

SUMMARY

Pain neuroscience education is currently one of the techniques being explored in physiotherapy for pain management. The benefits of this technique are gradually becoming evident in various published studies. So far, it has been widely studied for its short-term effects, but the education provided has typically been generic, not focused on exercise. However, it is suggested that this technique should be combined with exercise to achieve the expected outcomes. Therefore, pain education should be tailored to the specific physical activities the subject will perform to maximise its effectiveness. The primary aim of this study is to analyse the outcome of combining exercise with tailored pain neuroscience education on aspects such as pain, kinesiophobia, catastrophizing, exercise conceptualization, and upper limb function in subjects with neck pain. The secondary aim is to evaluate the relationship between kinesiophobia and catastrophizing and their impact on the results of various upper limb performance tests. Finally, the effects of therapeutic exercise alone will be compared with those of therapeutic exercise combined with pain neuroscience education, focusing on pain, kinesiophobia, catastrophizing, and exercise conceptualization. A double-blind, randomised clinical trial has been designed, in which three intervention protocols will be applied to 81 subjects with non-specific neck pain: education with exercise, exercise alone, and placebo alone. Subjects with non-specific neck pain who meet the inclusion criteria will be enrolled. Demographic characteristics of the subjects, as well as pain, kinesiophobia, catastrophizing, and upper limb performance test scores, will be assessed. This study aims to explore the potential relevance of a pain neuroscience education session prior to therapeutic exercise, as well as to influence the clinical recommendations made by clinicians during treatment.

INTRODUCTION

Neck pain is considered the fourth leading cause of disability (Cohen, 2015), with an age-standardised prevalence rate of 27 per 1,000 individuals in 2019 (Wu et al., 2024). Non-specific neck pain (NNP) is the most common type, and as the name suggests, the underlying mechanisms are unknown. However, it is proposed that musculoskeletal factors, such as deficits and alterations in proprioception of the neck muscles, which play a crucial role in motor control of the head and cervical joint positioning, may be involved in the maintenance, recurrence, and progression of pain (Treleaven, 2008). Furthermore, psychosocial factors such as catastrophising, kinesiophobia, stress, anxiety, and depression also play a significant role in influencing pain perception (Bushnell et al., 2013; Ortego et al., 2016). Therefore, as reflected in the current evidence, exercise and patient education are first-line interventions for managing NNP, receiving high levels of recommendation for all subtypes of non-specific neck pain, and across all stages of the condition, whether acute, subacute, or chronic (Bier et al., 2018; Blanpied et al., 2017).

Exercise has an analgesic effect on pain (Senarath et al., 2023). The most supported mechanism underlying the analgesic effects of exercise, according to the scientific community, is the activation of the endogenous opioid system during exercise of sufficient intensity. This hypothesis is based on the observation of the release of beta-endorphins, which are associated with an analgesic state (Goldfarb & Jamurtas, 1997; Stagg et al., 2011). However, exercise can also produce pain (Sluka et al., 2018). Moreover, patients with chronic pain often exhibit avoidant behaviours towards exercise and movement, a phenomenon known as kinesiophobia (Luque-Suarez et al., 2019). It is therefore not surprising that patients with chronic pain tend to be more inactive than those without pain (Dzakpasu et al., 2021). Additionally, these patients often present other altered psychosocial variables in relation to their pain, such as pain catastrophising (Thompson et al., 2010). These psychosocial symptoms, in turn, influence the perceived pain intensity and dysfunction (Thompson et al., 2010). Consequently, cognitive and emotional factors have a significant impact on pain perception (Bushnell et al., 2013), meaning that an intervention targeting these factors could modify both perceived pain and the analgesic effects of exercise.

In line with the previous discussion, Pain Neuroscience Education (PNE) is increasingly used as part of the treatment for patients with pain, especially in cases of non-specific low back pain (Clarke et al., 2011). This approach, in accordance with the biopsychosocial model, involves providing pain neuroscience information to the patient in order to enhance their understanding of their condition, change their beliefs, facilitate return to activity, and reduce unnecessary medical attention (Louw et al., 2016). The literature now recommends combining PNE with exercise, due to favourable results with this combination of therapies. However, there remains a need for further research in this field (Javdaneh et al., 2021).

NNP is often associated with upper extremity dysfunction (Osborn & Jull, 2013), as patients with severe neck pain or disability also report significant disability in the upper limbs (Mclean et al., 2010a). Furthermore, those patients with greater upper limb disability tend to avoid or abandon painful tasks due to the potential of pain (Ayre & Tyson, 2001; Levin et al., 1996).

Additionally, when patients believe that pain is directly linked to injury or tissue damage, they exhibit a reduced ability to control this pain (Louw et al., 2016). This observation supports the notion that patient beliefs not only influence pain intensity but also their level of disability. Thus, pain neuroscience education may have a positive effect on pain intensity, dysfunction levels, and fear of movement, particularly when combined with therapeutic exercise (Louw et al., 2011).

Most of the current scientific evidence regarding pain neuroscience education (PNE) has been explored in patients with chronic low back pain, with less focus on other types of pain, such as NNP. Consequently, there is less information available to support the role of education combined with exercise for these patients, particularly in terms of perceived pain, kinesiophobia, catastrophising, and even the conceptualisation of exercise itself. The potential relationship between upper extremity dysfunction, as measured by functional or performance tests, and the aforementioned parameters is also not extensively studied.

Addressing these issues is the primary motivation for conducting the present study.

JUSTIFICATION AND OBJECTIVES

In recent years, education in pain neuroscience has been shown to have a positive impact on pain subjects. However, the education provided is often generic and not adapted to exercise, although it is recommended that this therapy should be combined with exercise. Therefore, the aim of this study is to assess the results of the combination of exercise and pain neuroscience education focused on the exercise to be performed by subjects in pain or kinesiophobia. Therefore, the main objective of the study is to evaluate the effects of pain neuroscience education in non-specific neck pain on pain intensity, kinesiophobia, catastrophizing, exercise conceptualization and upper limb functionality itself in subjects with non-specific neck pain. The specific objective is to compare the effect of therapeutic exercise alone with the effect of therapeutic exercise in combination with pain neuroscience education on pain, kinesiophobia, catastrophizing and exercise conceptualization. Similarly, the aim is to determine the relationship between kinesiophobia and catastrophism and the results obtained in upper limb performance tests. For this purpose, the Closed Kinetic Chain Upper Extremity Stability Test (CKCUEST), the Seated Medicine Ball Throw test (SMBT) and the Single Arm Military Press (SAMP) have been chosen, the first two of which have not been studied in patients with non-specific neck pain to date. This study aims to have an impact on the possible relevance of a pain neuroscience education session prior to therapeutic exercise, as well as on the clinical recommendations made by healthcare professionals during treatment.

DESIGN

The study consists of a randomised, double-blind clinical trial. Subjects will be randomised into 3 groups: control group, where subjects will receive a placebo (TENS off, in this case); intervention group 1, where pain neuroscience education (PNE) and exercise will be applied; and intervention group 2, to which only exercise will be applied. The allocation will be blinded to the subject and to one of the two investigators.

SELECTION CRITERIA

Inclusion criteria: o Adults aged between 18 and 65 years. o Subjects with non-specific neck pain at the time of the intervention reaching at least a 3 on the

Numerical Pain Rating Scale (NPRS scale). Exclusion criteria: o Pregnancy o Severe illnesses: diabetes, cancer, neurological, depression, etc... o Cognitive disorders or illnesses. o Subjects who have received physiotherapy treatment in the last month. o Subjects who are receiving concomitant physiotherapy treatment for this pathology. o Subjects with specific neck pain, such as any traumatic pathology, whiplash or with a diagnosis associated with neurological compromise or peripheral nerve damage. o Physiotherapy students or professional physiotherapists. Subjects included in the study must complete the informed consent form, meet the inclusion criteria and not meet the exclusion criteria. Prior to any type of procedure, subjects will be informed about the study and about their right to discontinue their participation and/or request the withdrawal of their data at any time.

DESCRIPTION OF THE PROCEDURE

At the beginning, all subjects will sign the informed consent form, demographic data will be recorded by means of an interview and a questionnaire specifically designed for the work. After that, baseline measurements of outcome variables will be taken. Fear of movement and kinesiophobia will be measured with the Tampa Scale of Kinesiophobia (TSK- 11SV), pain catastrophizing with the Pain and Castastrophizing Scale (PCS), and subject's beliefs about pain with the Pain Beliefs Questionnaire (PBQ). The Spanish validated versions of all the aforementioned scales will be used. The Numerical Pain Rating Scale (NPRS) will be used to assess subjects' current pain and spontaneous or evoked pain intensity. Researcher A will then show each subject images of the 3 performance tests they will have to perform, as well as provide an explanation of their execution: Closed Kinetic Chain Upper Extremity Stability Test (CKCUEST), Single Arm Military Press (SAMP) and Seated Medicine Ball Throw Test (SMBT). Regardless of whether subjects are later assigned to the exercise group or not. These tests are among the most widely used tests to measure upper limb function, although they have not been studied in subjects with non-specific neck pain. The Single Arm Military Press (SAMP) test is the only performance-based measure of upper limb disability that was designed specifically for subjects with neck pain. All these tests involve active movements that could be conditioned by the subject's pain and beliefs related to kinesiophobia, so they could be of great use to observe whether an educational approach decreases upper limb dysfunction. Finally, subjects' beliefs about the exercises explained in relation to their pathology will be assessed by means of a questionnaire specifically designed for this purpose. After this procedure is completed by all participants, they will be randomised into three groups, using a randomisation website (Research Randomizer, n.d.) and will undergo a physiotherapy session that includes different approaches for each group.

In the PNE and exercise group the investigator will proceed with pain neuroscience education focused on concepts related to movement-related fear and the benefits of exercise for 20 minutes. Specifically, the exercises presented in the generic part of the procedure will be discussed. To assess whether the education has resulted in changes to the subjects’ beliefs, they will be reassessed

regarding their beliefs about the exercises in relation to their neck pain following the education session. Afterward, subjects will complete psychosocial scales and rate their pain and evoked pain at that moment independently, without the need for the researcher to be present, in order to ensure blinding. Subsequently, the subject will undergo the performance tests in a randomised order (Closed Kinetic Chain Upper Extremity Stability Test, Single Arm Military Press, and Seated Medicine Ball Throw), which will be conducted by a second investigator who is unaware of whether the subject has received education. The exercise intervention will then proceed using variations of the performance tests, also carried out by the second investigator. Specifically, the load or execution time will be increased until the participant reports a perceived fatigue of 4-6 (moderate to strong) on the modified Borg scale. Finally, the participant will autonomously complete the scales, rate their pain and exercise-related questions for the final time.

The exercise group does not include pain neuroscience education. Following the initial assessment, the subject will be left alone for 20 minutes with instructions to think about the exercises but not to perform them. Afterward, subjects will complete psychosocial scales and will rate their pain and evoked pain at that moment independently, without the need for the researcher to be present, in order to ensure blinding. Subsequently, the subject will undergo the performance tests in a randomised order (Closed Kinetic Chain Upper Extremity Stability Test, Single Arm Military Press, and Seated Medicine Ball Throw), which will be conducted by a second investigator who is unaware of whether the subject has received education. The exercise intervention will then proceed using variations of the performance tests, also carried out by the second investigator. Specifically, the load or execution time will be increased until the participant reports a perceived fatigue of 4-6 (moderate to strong) on the modified Borg scale. Finally, the participant will independently complete the scales, rate their pain, evoked pain, and exercise-related questions one final time.

The control group doees not receive pain neuroscience education or exercise. Following the initial assessment, the subject will be left alone for 20 minutes with instructions to think about the exercises but not to perform them. Afterward, subjects will independently complete psychosocial scales and will rate their pain and evoked pain at that moment, without the need for the researcher to be present, in order to ensure blinding. Subsequently, participants in this group will receive a placebo intervention administered by a second investigator. A TENS device will be placed on them and kept turned off for 15 minutes. subjects will be informed that the device is operating at a very low intensity, too weak to be perceived. Additionally, performance tests will not be assessed in this group. Finally, the participant will autonomously complete the scales, rate their pain and exercise-related questions for the final time. Therefore, all groups will be assessed 3 times during the session. The first time they will be accompanied by the first investigator, who will answer any questions that may arise. The second and third time the subject will do it autonomously, unaccompanied by any researcher, to avoid bias.

OUTCOME MEASURES

Primary oucome measures

Kinesiophobia: The level of kinesiophobia will be assessed using the Tampa Scale for Kinesiophobia (TSK-11SV). This scale evaluates kinesiophobia (fear of movement) through 11 statements, which participants must rate on a Likert scale from 1 to 4, where 1 indicates strongly disagree and 4 indicates strongly agree. Higher scores reflect greater kinesiophobia (minimum score: 11; maximum score: 44). The validated Spanish version of the scale will be used. Measurements will be collected at baseline, after the education session or waiting period (depending on the assigned group), and after the exercise intervention or placebo (depending on the assigned group).

Pain beliefs: Pain beliefs will be assessed using the Pain Beliefs Questionnaire (PBQ), which evaluates beliefs regarding the causes, consequences, and necessary treatment of pain. The questionnaire is divided into two subscales: "organic" and "psychological." It consists of 12 items, with 8 items belonging to the "organic" subscale and 4 to the "psychological" subscale. The PBQ uses a 6-point Likert scale ranging from "Always" to "Never," corresponding to scores of 6 and 1, respectively. Higher scores on each subscale indicate that the respondent considers the corresponding pain-related beliefs to be of greater importance. Measurements will be collected at baseline, after the education session or waiting period (depending on the assigned group), and after the exercise intervention or placebo (depending on the assigned group).

Catastrophizing: The level of catastrophizing will be assessed using the Pain and Catastrophizing Scale (PCS). This scale evaluates catastrophizing in response to pain and the negative and exaggerated perception of the painful experience. It consists of 13 statements describing different thoughts and feelings that may be associated with pain. The participant is required to indicate the extent to which they experience these thoughts and feelings when they are in pain. Each statement is rated on a Likert scale from 0 to 4, where 0 means "not at all" and 4 means "all the time." Higher scores indicate a higher degree of catastrophizing. The validated Spanish version of the scale will be used. Measurements will be collected at baseline, after the education session or waiting period (depending on the assigned group), and after the exercise intervention or placebo (depending on the assigned group).

Pain intensity: Pain intensity will be assessed using the Numerical Pain Rating Scale (NPRS). This scale evaluates the intensity of pain experienced by the participant, using a 10-point scale, where 0 represents no pain and 10 represents the maximum possible pain. Higher scores correspond to greater pain intensity. Measurements will be collected at baseline, after the education session or waiting

period (depending on the assigned group), and after the exercise intervention or placebo (depending on the assigned group).

Evoked pain intensity: Evoked pain will be assessed using the Numerical Pain Rating Scale (NPRS). Participants will be asked to perform a movement that evokes pain related to their condition. Pain intensity will then be evaluated on a 10-point scale, where 0 represents no pain and 10 represents the maximum possible pain. Higher scores correspond to greater pain intensity. Measurements will be collected at baseline, after the education session or waiting period (depending on the assigned group), and after the exercise intervention or placebo (depending on the assigned group).

Secondary outcome

Demographic data: Participants will complete a demographic questionnaire, including descriptive variables such as age, sex, weight, height, level of physical activity, comorbidities, duration of pain, side of pain, and smoking status. **Data Will be collected** at baseline (before any intervention).

Beliefs about specific exercises: Beliefs about specific exercises in relation to pain will be assessed using a custom questionnaire. The questionnaire evaluates the participants' beliefs regarding the specific exercises they will perform. Participants will first be shown photographs of the exercises they are required to do, and then they will respond to the questionnaire by selecting a number on a visual analogue scale from 1 to 10, where 1 indicates "strongly disagree" and 10 indicates "strongly agree." Higher scores reflect stronger beliefs about the exercises in relation to their pain. This questionnaire was specifically designed for this study and is being used for data collection. Measurements will be collected at baseline, after the education session or waiting period (depending on the assigned group), and after the exercise intervention or placebo (depending on the assigned group).

Pain intensity and worst pain intensity over last 7 days: Pain intensity will be assessed using the Numerical Pain Rating Scale (NPRS). This scale evaluates both the average and worst pain intensity experienced by the participant over the last 7 days, using a 10-point scale where 0 represents no pain and 10 represents the maximum possible pain. Higher scores correspond to greater pain intensity. **Data Will be collected** at baseline (before any intervention).

Functional performance of the upper extremities (CKCUEST): Functional performance of the upper extremities will be assessed using the Closed Kinetic Chain Upper Extremity Stability Test (CKCUEST), a test designed to evaluate

upper limb stability and control. During the test, male participants will adopt a push-up position, while female participants will assume a modified push-up position (knees on the ground). Both hands will be placed on two strips on the floor at the same height, with a distance of 91.4 cm between them. In these positions, participants will be required to move one hand to touch the back of the opposite hand, then return to the starting position, repeating the movement with the other hand, for 15 seconds. The test will be performed for three 15-second repetitions at maximum effort, with a 45-second rest between each repetition. The outcome measure will be the average number of touches (mean of the number of touches from the three attempts). Data Will be collected after the education session or waiting period (depending on the assigned group) for the Education and Exercise and Exercise groups

Functional performance of the upper extremity (SAMP test): Functional performance of the upper extremity will be assessed using the Single Arm Military Press (SAMP). This performance-based measure is designed to assess upper extremity strength during an overhead activity, aimed at differentiating between healthy individuals and those with varying levels of nonspecific neck pain and upper extremity disability. The exercise is performed with participants standing, with their feet shoulder-width apart, holding a 1 kg dumbbell at shoulder height with their dominant hand. Participants are instructed to lift the dumbbell overhead, performing a full shoulder flexion and elbow extension. The test consists of repeating this motion as quickly as possible for 30 seconds with maximal effort. The SAMP score is determined by counting the number of correct repetitions completed in 30 seconds. The test is stopped if the participant is unable to complete another correct repetition. Data Will be collected after the education session or waiting period (depending on the assigned group) for the Education and Exercise and Exercise groups.

Functional performance of the upper extremities (SMBT): Functional performance of the upper extremities will be assessed using the Seated Medicine Ball Throw Test (SMBT). Participants will sit with their back against the wall, legs extended, holding a 2 kg medicine ball with arms at 90° shoulder abduction and elbows flexed at chest height. They will throw the ball forward as far as possible without losing contact with the wall. The distance will be measured by a tape placed 10 meters from the subject's starting point. Three maximum effort throws will be performed with 1-minute rests between each, and the result will be the average of the three throws. Data Will be collected after the education session or waiting period (depending on the assigned group) for the Education and Exercise and Exercise groups

HYPOTHESIS

We hypothesize that pain neuroscience education focused on movement and exercise will significantly reduce both kinesiophobia and catastrophising, as well as improve the conceptualisation of exercise and upper limb functionality. Therefore, pain neuroscience education will modify the subjects' beliefs regarding exercise participation.

Additionally, the group receiving both education and exercise will achieve better performance test results compared to the group that only receives exercise and the placebo group.

SAMPLE SIZE

To perform the sample size calculation, an independent measures ANOVA was used on the primary variable: the Tampa Scale of Kinesiophobia (TSK-11SV). The effect size estimation was based on a previous study with an experimental design similar to our proposed one (Beltran-Alacreu et al., 2015). We used G*Power 3.1.14 software (Erdfelder et al., 2009; Faul et al., 2007). An effect size of F = 0.36 was estimated for the primary variable (TSK-11SV), assuming a random error of 5% and a minimum statistical power of 80%. The result was a sample size of 27 subjects per group, i.e., 81 subjects in total.

STADISTICAL ANALISIS PLAN

Once all data have been coded, the normality of the distribution will be assessed using the Shapiro-Wilk test and histogram visualisation. If the data do not follow a normal distribution, the corresponding non-parametric tests will be used instead.

To examine changes in the variables for each protocol, pre-intervention measurements will be compared with post-intervention measurements within each protocol. A repeated measures ANOVA will be used for this comparison (or the Friedman test if normality is not met).

To determine whether the intervention groups differ from the TENS control group or from each other, a two-way ANOVA will be performed. This analysis will consider the within-subjects factor (time), the between-subjects factor (intervention), and their interaction. If normality is not met, the corresponding non-parametric test (Kruskal-Wallis) will be conducted.

If significant differences are found in the ANOVA tests, post hoc comparisons will be explored using Dunnett's or Bonferroni tests, depending on the nature of the comparison.

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